CONCURRENT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED NASOPHARYNGEAL CARCINOMA; USING CISPLATIN PLUS 5-FU, AT PHRAMONGKUTKLAO HOSPITAL

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ABSTRACT

Twenty nine patients with locally advanced nasopharyngeal carcinoma were treated at Phramongkutklao hospital during 1993 and 1995, by concurrent chemoradiotherapy and adjuvant chemotherapy. Chemotherapy regimen consisted of Cisplatin 100 mg/m^2 on day 1 plus 5-FU 800 mg/m^2 as continuous infusion on day 1 to 4 and repeated every 28 days for 6 cycles. Radiation treatment using Cobalt-60 and 10 MV photon or electron beam to boost primary site or cervical node until a total dose reached 6000-7000 cGy/6.6-8 weeks. Initial complete and partial response rate at 4 or 8 weeks after completion of radiotherapy were 67.9% and 28.6% respectively . At one month after completion of the sixth course of chemotherapy; complete response rate was increased to 75%. With a median follow up period of 42.2 months after completion of radiotherapy course, 3 year and 5 year actuarial survival rate(by Kaplan-Meier method) were 71% and 64% respectively. Toxicity from the treatment was acceptable. **In conclusion**, the concurrent chemoradiotherapy using cisplatin and 5-FU for locally advanced nasopharyngeal carcinoma was feasible and effective without any serious side effects.

INTRODUCTION

Nasopharyngeal carcinoma is one of the most highly malignant tumors of the head and neck region. At Phramongkutklao hospital, it was the eighth leading site of cancer in the year 1993 and 1994.[1] (approximately 4% of all cancers found in this hospital) Even though high survivval rates can be achieved with radiation therapy alone for early stage lesions,the control of advanced disease is poor.[2,3] Advanced disease at the primary site presents problems in local control, and the risk for distant metastasis is known to be particularly high with extensive nodal disease. The most common sites of metastatic disease are bone(70%), liver (50%) and lung(47%), with 48% of patients concomitantly developing metastasic disease in all three sites.[5] Local and regional recurrences remain the major cause of death and distant metastasis is a cause of significant morbidity and mortality as well.

In an attempt to improve locoregional control and reduce distant metastasis, several phase II trials showed that nasopharyngeal carcinoma was highly sensitive to induction chemotherapy with response rate ranging from 75-98%.[6] However, it has not been determined whether excellent response to chemotherapy could be translated into survival benefit in nasopharyngeal cancer.[7,8,9,10,11,12] Adjuvant chemotherapy after radiation treatment was used for the advantage of decreasing metastasis, but the benefit for prolonging survival cannot be firmly established.[13,14,15,16] Concomitant chemotherapy and radiotherapy has been studied with complete response rate around

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60-100%.[17,18,19,20,21,22,23,24,25,26] The goals of simultaneous administration of chemotherapy and radiotherapy are to enhance the radiotherapy and improvement of the locoregional control rate and to eradicate early systemic (micrometastasis) disease.

We studied the results using chemotherapy (cisplatin and 5 FU) concurrently with radiotherapy in the treatment of locally advanced nasopharyngeal carcinoma. The response rate, survival and toxicity from the treatment were reported.

MATERIAL & METHODS

From 1993 to 1995; 29 patients with locoregionally advanced nasopharyngeal carcinoma were treated with concurrent chemoradiotherapy. The chemotherapy regimen consisted of cisplatin 100 mg/m^2 given on day 1 plus 5 FU 800 mg/m^2 as a continuous infusion on day 1 to 4 of radiotherapy course and repeated every 28 days for 6 cycles.

Radiotherapy was delivered using a telecobalt unit for the first 4500-5000 cGy with a daily dose of 180-200 cGy. The spinal cord was excluded after 4400-4500 cGy and electron beam boost to posterior cervical chain nodes was given until 5000 cGy. The 10 MV photon was used to boost primary tumor until a total dose reached 6000-7000 cGy.(180-200 cGy/ fraction) The bulky nodal area was boosted by electron beam of appropriate energy until a total dose reached 6600-7000 cGy. The hyperthermia was applied twice weekly, 72 hours interval, to the large cervical node in some patients during the course of radiotherapy.

All 29 patients had a biopsy proof of malignancy in nasopharynx, and were staged according to American Joint Committee TNM staging system 1992. The patients' characteristic were shown in table 1.

Table 1 Patients' characteristic

Total numbers of patients	29	cases
Male	22	cases (75.86%)
Female	7	cases (24.14%)
Median age	43.7	year (22-65 year)
Symptoms at presentation		
Neck mass	11	cases (37.9%)
ear symptoms	9	cases (31.1%)
nose symptoms	4	cases (13.8%)
head ache	3	cases (10.4%)
diplopia	1	case (3.4%)
mass at palate	1	case (3.4%)
Histology		
Undifferentiated CA (WHO type III)	18 cases (62.1%)	
Non keratinized CA (WHO type II)	11 cases (37.9%)	

T and N distribution

N \ T	T1	T2	T3	T4	Total
N0	0	0	2	11	13
N1	0	1	1	1	3
N2	0	3	1	1	5
N3	0	4	1	3	8
Total	0	8	5	16	29

RESULTS

The median age of the patients was 43.7 year. (range from 22 to 65 year) Male patients were predominant. (75.86%) Most of the patients were staged in T4N0. (11 cases, 37.9%) Eighteen patients (62.1%) were undifferentiated carcinoma. (WHO type III)

Among 29 patients, one case was lost to follow up during radiotherapy course and was excluded from the analysis. Two patients did not receive full course of chemotherapy after completetion of the radiation treatment. One patient did not have a follow up after completion of the sixth course of chemotherapy. These three patients were still included in the study. All 28 patients were followed up ranging from1 month to a maximum of 62 months after completion of the course of radiotherapy. The median time of follow up was 42.2 months. The initial response to the treatment was evaluated by indirect nasopharyngoscopy, cervical node palpation, or CT scan in some cases at one or two months after completion of radiation treatment, and reevaluated again at 1 month after the sixth course of chemotherapy. The initial complete response rate (CR) and partial response rate (PR) were 67.9% (19 in 28 cases) and 28.6% (8 in 28 cases) respectively. At one month after having completed the sixth course of chemotherapy, the CR rate was increased to 75%. (21 in 28 cases)

Recurrent diseases were found in 10 cases during follow up period. Pattern of recurrences were shown in table 2.

Table 2 Pattern of recurrent diseases

NO.	sex	age	histology	T N	Site of recurrence and time from complete RT (months)			
					primary	node	metastasis	Status
1	F	55	UD	3 2	+(36)			A
2	M	35	UD	4 0	+(16)			D
3	F	27	UD	2 3	+(51)	+(33)		A
4	M	34	NK	4 0	+(18)		bone(19)	D
5	M	35	NK	2 3	+(15)			D
6	F	42	UD	4 3		+(12)	bone(15)	D
7	M	59	UD	2 2		+(30)		A
8	M	49	UD	2 3			lung(24)	D
9	M	52	UD	3 1			bone(29)	A
10	M	64	UD	4 0			bone(15)	D

M = male, F = female; UD = undifferentiated CA, NK = non-keratinized; A = alive, D = dead

Among these patients, 6 cases died. Two of them died because of recurrence at primary sites; two from metastasis (lung, bone); one from cervical node recurrence with bone metastasis; and one from recurrence at primary site with bone metastasis.

By Kaplan-Meier method,3 year and 5 year actuarial survival rate were 71% and 64% respectively.

Toxicities from the treatment according to RTOG grade were found in patients during radiotherapy course as shown in table 3.

Table 3 Number of cases and RTOG grade from treatment

	RTOG toxicity grade				
	0	1	2	3	4
WBC	9	11	5	3	0
PMN	19	3	3	3	0
Hb	13	8	7	0	0
Hct	13	8	2	0	0
Platelet	24	2	1	1	0
Mucositis	0	19	1	8	0

Most of the toxicities were grade 1 or 2. We did not find the grade 4 toxicity. Grade 3 leukopenia, neutropenia, and mucositis were found in some cases, ranging from 10.7% to 28.6%. (as shown in table 4)

Table 4 RTOG toxicity grade 3

WBC < 2,000/cu.mm	3/28 cases (10.7%)
PMN < 1,000/cu.mm	3/28 cases (10.7%)
Mucositis	8/28 cases (28.6%)

All patients who had toxicities from the treatment recovered after supportive treatment. No one died from complication. The grade 3 toxicities led to treatment interruption during radiotherapy course ranging from 2 days to a maximum of 32 days. For three patients with a breaking period up to 14 days, recurrent diseases at primary site, nodal area or metastasis were noted. They all died during follow up period. Seven patients had a breaking period longer than 14 days. In this group, two died from bony metastasis and primary site recurrence, one had a recurrence at primary and nodal area but still alive at 51 months of follow up, two cases were free from disease at 35 and 45 months, the last two cases lost contact at 1 and 4 months after completion of radiotherapy.

DISCUSSION

The use of chemoradiotherapy for regionally advanced head and neck cancer has been tested over many years. Two major goals have been pursued: to increase the overall survival rates and to decrease the morbidity of standard treatment, and to minimize the need for radical surgery. (organ preservation)[27] There are three general approaches; induction (neoadjuvant) chemotherapy, adjuvant chemotherapy and concomitant chemotherapy with radiation treatment. Since nasopharyngeal carcinoma cells are also chemosensitive, chemotherapy has been used increasingly in the treatment of advanced nasopharyngeal carcinoma, in assosiate with radiotherapy.

The exact interaction of platinum compounds and radiation to enhance cell death is not completely understood. Possible mechanisms for enhancing radiation effects include inhibition of repair of sublethal damage, selective radiosensitization of hypoxic cells, and reduction of tumor bulk, resulting in impaired tumor blood supply, reoxygenation, and recruitment of cells into a more radiosensitive proliferative phase.[28] The response to cisplatin-based combination is considered superior to noncisplatin combination chemotherapy in patients with recurrent or metastatic nasopharyngeal carcinoma.[29] This has led to the use of cisplatin alone or combined with 5-FU with radiation therapy in patients with previously untreated nasopharyngeal carcinoma. Many studies do not show the results that significantly translate into improved survival. Until 1990; Al - sarraf et al[21] reported the results of concurrent radiotherapy and cisplatin in locally advanced nasopharyngeal cancer which showed disease free survival, overall survival and the incidence of distance metastasis appeared to be better than patients treated with radiotherapy alone. The same result was shown by Giri in 1996,[30] with 3 year survival being better in chemoradiotherapy group v.s. radiotherapy group.(76% v.s. 44%) The major problem that made the out come of treatment in combined group not superior to radiotherapy alone in many studies was the development of mucositis or myelosuppression toxicities which resulted in a breaking period during the course of radiation treatment leading to the prolongation of the overall treatment time.[19,23,24] Amdur et al[31] retrospectively compared patients treated with continuous course of radiation therapy with those who had a protracted course (usually because of toxic events), and reported a significant difference in local control and survival favoring patients who had uninterrupted radiation. Wang and colleagues[32] showed the effect of interruption of treatment longer than 14 days and and overall treatment time longer than 45 days resulted in the lower local control rate when compared to the over all treatment time less than 45 days. (57% v.s. 77%)

Our data showed the acturial 3-year and 5- year survival rates (by Kaplan - Meier method) of 71% and 64% respectively, which were comparable to results reported by Giri et al.[30] The CR rate that seemed to be low in our study could be explained by high percentage of patients classified as T4 (38%) that led to the poor outcome of treatment. Most of the toxicities from the treatment were mucositis, neutropenia and leukopenia grade II which were reversible after a rest period during the radiotherapy course. No one died from complication. Locoregional failures were found in 5 cases. Distance metastasis were found in 5 cases, most were bony metastases. The braking period during the radiotherapy course for at least 14 days was seem to be one of the factor that contributes to treatment failure, but, due to limited number of cases, it was still controversial to make a definite correlation.

In conclusion, concurrent chemoradiotherapy, using cisplatin and 5-FU, was effective in the treatment of locally advanced nasopharyngeal carcinoma with acceptable toxicity. However, limitation in number of cases and poor compliance in patients' follow up were still the major problems of analysis to draw a firm conclusion in the results obtained in our study. Further studies in a phase III randomized trial are warranted.

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